GE Healthcare

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Documents Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 1061
Rockville, MD 20852

**Re: Docket No. 2005D-0122**
**Comments to Draft Guidance – Exploratory IND Studies**

Dear Documents Management Staff:

Reference is made to the subject docket number published in the Federal Register Volume 70, Number 71, page 19764 which announced the availability of a draft guidance for Industry, Investigators and Reviewers entitled "Exploratory IND Studies."

At this time, as requested by the Federal Register notice, GE Healthcare is providing its comments to the draft guidance on the following pages.

Please call me at (609)-514-6573 if you have any questions or comments regarding this submission.

Sincerely,
GE Healthcare

Fred Longenecker
Director, Regulatory Development

2005D-0122 C5

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**Guidance for Industry, Investigators, and Reviewers**

**Exploratory IND Studies – Draft Guidance – April 2005**

**(Docket No. 2005D-0122)**

**GE Healthcare Comments**

## General Comments

GE Healthcare strongly welcomes this initiative from the FDA. It is largely consistent with our own thinking and we would like to suggest that some of the concepts in this document could be further elaborated to enable a simple transition from an exploratory IND to the "standard" IND when applied to a radiopharmaceutical agent. See our further comments below. We note and welcome the emphasis placed by the agency on flexible approaches to the early development of agents.

We note that this draft guideline was written without specific reference to radiopharmaceutical agents; however, the concept of dosing at sub-pharmacological effect is inherent in the development of a diagnostic radiopharmaceutical. Hence much of the microdosing study design, intending to study pharmacokinetics in small numbers of patients, as described in this draft, is the usual development pathway for diagnostic radiopharmaceuticals.

We note that throughout the document the Agency indicates that studies performed under the exploratory IND should have "no therapeutic intent" – however it is true to say that no imaging agent has a "therapeutic intent" but that for many – certainly for diagnostic radiopharmaceuticals – the intent of these early studies will be to determine whether the agent is capable of imaging the target lesion (or biological system) and also provides adequate background clearance. This is the way these drug products work and hence we are, by definition, studying the intended use of the products in evaluating whether they should progress to full development. Consequently, it would be useful to have further explanation as to what is meant by "no therapeutic intent" as applied to imaging agents. It would also be useful to understand the extent to which these early studies could be used (or extended) to permit the subsequent reduction of the need for additional studies.

Given the special features of diagnostic radiopharmaceuticals mentioned above, it may be helpful for the Agency to include reference to how the exploratory IND guideline may be applied to development of these types of products in the guideline itself.

Some consideration might usefully be applied to how this guidance may also ease the burden on early development/lead selection for contrast agents but here the scope is generally less with the possible exception of the up and coming optical imaging area.

**Specific comments**

Line 23 - Could the agency provide some clarification regarding the statement in line 23 which refers to "closely related drugs"? Is this intended to imply the use of radiolabelled drugs to investigate the disposition of a therapeutic analogue or can this principle be applied to the study of a class of imaging agents with minor structural differences based on the safety profile of a single model compound from the class?

Lines 34-36 - Does the statement "Such exploratory IND studies are conducted prior to traditional dose escalation, safety and tolerance studies that ordinarily initiate a clinical development program." mean that such "traditional" studies must be conducted under a "standard" IND that is a direct follow-on to an exploratory IND? We assume that it will be possible to generate some of these data, such as radiation dosimetry data (for radiopharmaceuticals), from the Exploratory IND studies and hence preclude further unnecessary exposure of volunteers to radiation in dosimetry studies conducted under an IND that follows. Also we understand from recent interactions with the Agency that "traditional" dose escalation studies are NOT required for diagnostic radiopharmaceuticals where this can be adequately justified based on data from other studies.

Lines 103-107 - We note that the aspects mentioned in bullets in lines 103 and 107 as being suitable for study under an exploratory IND but described in the text as having no therapeutic intent, are directly related to the "therapeutic intent " of an imaging agent, as the usefulness of an imaging agent depends on the pharmacokinetics of the molecule .

Lines 114-115 – It is stated that, "The studies studies discussed in this guidance involve dosing a limited number of subjects with a limited dose range and for a limited period of time." In practice this statement describes the standard IND phase 1 and phase 2 clinical trials of diagnostic radiopharmaceuticals (in particular PET agents). Would the Agency agree that the preclinical and limited dose ranging clinical programs performed as phases 1 and 2 clinical studies for diagnostic radiopharmaceuticals, could be performed under an exploratory IND (and hence would not need to be repeated under a 'standard' IND) and that a company may proceed directly to phase 3 under a supplemented IND.

Lines 119-126 – It is stated that, "... exploratory IND studies involve administering either sub-therapeutic doses of a product. " The reference to "sub-therapeutic" applies equally to the commercial clinical dose of radiopharmaceuticals and some contrast agents (such as optical imaging agents). In light of this would the agency agree that for these agents the highlighted statement in lines 123-126 is equally applicable to the full IND programme in certain clearly justified cases – such as for PET imaging agents? By definition imaging agents (especially radiopharmaceuticals) are designed not to have a pharmacological effect – otherwise they would change the parameter they are designed to measure rather than measuring it accurately, Thus it seems illogical to expect a higher degree of safety/pharmacology work to be necessary moving into the follow-on "standard" IND program than was necessary at the exploratory IND phase.

Line 152 – The bullet in this line requires the submission of a clinical development plan and further guidance is provided in lines 168 to 177. Do the required introductory statement and general investigational plan need to address the issue of clinical need?

Lines 158-159 - It is stated that studies under an exploratory IND would be the first use in man and hence previous clinical experience is not relevant. We would suggest that if a company were to develop an imaging agent based on an existing therapeutic drug then in some instances the company should be able to rely on a wealth of safety data on the closely related compound. Can the FDA confirm our understanding on this point?

Lines 172-173 - We welcome the statement that a sponsor may provide a rationale for studying several compounds in the same clinical trial.

Lines 310-315 - The definition of a microdose and the rationale for microdose studies in lines 310-313 can be applied to diagnostic radiopharmaceuticals, where a very low chemical dose, designed not to induce pharmacological effects, is administered as the commercial dose. This very low chemical dose is particularly relevant to PET agents where doses will never exceed the microdose level. We understand the guideline to say that the safety program outlined in the draft to support an exploratory IND would be acceptable to support microdose clinical studies, therefore we ask the Agency to clarify this in relation to the final Guidance for Industry on Developing Medical Imaging Drug and Biological Products - Part 1: Conducting Safety Assessments (June 2004). If the exposure in normal clinical use will be similar there should be no need to perform any additional preclinical studies. In particular there should be no need at any stage to perform safety pharmacology as lines 366 – 370 refer to safety pharmacology being required where the exploratory IND study is designed to elicit pharmacological effects.